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Topographic distribution of white matter changes and lacunar infarcts in neurodegenerative and vascular dementia syndromes: A post-mortem 7.0-tesla magnetic resonance imaging study

Jacques De Reuck, Florent Auger, Nicolas Durieux, Charlotte Cordonnier, Vincent Deramecourt, Florence Pasquier, Claude-Alain Maurage, Didier Leys and Regis Bordet

Abstract

Background: White matter changes and lacunar infarcts are regarded as linked to the same underlying small-vessel pathology. On magnetic resonance imaging, white matter changes are frequently observed, while the number of lacunar infarcts is probably underestimated. The present study post-mortem 7.0-tesla magnetic resonance imaging study compares the severity and the distribution of white matter changes and lacunar infarcts in different neurodegenerative and vascular dementia syndromes in order to determine their impact on the disease evolution.

Patients and methods: Eighty-four post-mortem brains consisting of 15 patients with pure Alzheimer's disease and 12 with associated cerebral amyloid angiopathy, 14 patients with frontotemporal lobar degeneration, 7 with Lewy body dementia, 10 with progressive supranuclear palsy, 14 with vascular dementia and 12 control brains were examined. Six hemispheric coronal sections of each brain underwent 7.0-tesla magnetic resonance imaging. Location and severity of white matter changes and lacunar infarcts were evaluated semi-quantitatively in each section separately.

Results: White matter changes predominated in the prefrontal and frontal sections of frontotemporal lobar degeneration and in the post-central section of associated cerebral amyloid angiopathy brains, while overall increased in vascular dementia cases. Lacunar infarcts were more frequent in the vascular dementia brains and mainly increased in the centrum semiovale.

Conclusions: White matter changes have a different topographic distribution in neurodegenerative diseases and are most severe and extended in vascular dementia. Lacunar infarcts predominate in the deep white matter of vascular dementia compared to the neurodegenerative diseases. Vascular cognitive impairment is mainly linked to white matter changes due to chronic ischaemia as well as to lacunar infarcts due to small-vessel occlusion.

Keywords

Post-mortem 7.0-tesla MRI, white matter changes, lacunar infarcts, neurodegenerative diseases, vascular dementia

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Introduction

White matter changes (WMCs) and lacunar infarcts (LIs) are regarded as linked to the same underlying small-vessel pathology.[1] Positron emission tomography studies have shown that the WMCs are due to diffuse ischaemic damage.[2] In LIs thickening of the arterial media and obstruction of the origins of penetrating arteries by parent artery intimal plaques are the major underlying vascular pathologies.[3]

In-vivo magnetic resonance imaging (MRI) studies show frequently WMCs in elderly persons,[4–7] but probably underestimate the number of lacunes.[8]

Université Lille 2, INSERM U 1171, Lille, France

Corresponding author:
Jacques De Reuck, Leopold II laan 96, BE-9000 Ghent, Belgium.
Email: dereuck.j@gmail.com

LIs can change in size and even become invisible with time on conventional neuroimaging.[9] Only diffusion-weighted MRI imaging, performed within five days, allows demonstration of the responsible lesion in the classical lacunar syndromes.[10]

There is a need to determine whether there are differences in the severity and topography of WMCs and LIs between the different neurodegenerative and cerebrovascular diseases, leading to dementia. In our previous post-mortem MRI study, with neuropathological correlates, cortical micro-infarcts of different sizes were not only increased in brains of patients with vascular dementia but also in those with Alzheimer dementia, associated to cerebral amyloid angiopathy and Lewy body dementia.[11]

The present study, post-mortem 7.0-tesla MRI study, compares the severity and the distribution of WMCs and LIs in different neurodegenerative and vascular dementia syndromes in order to determine their impact on the disease evolution.

Materials and methods

Between November 2010 and 2014, all 84 autopsied patients followed up at the Lille University Hospital, underwent post-mortem 7.0-tesla MRI examination of six serial hemispheric brain sections, followed by an extensive histological examination of the brain samples. The final disease diagnosis was made according to the validated neuropathological criteria.[12] The cohorts consisted of 15 patients with pure Alzheimer's disease (AD) and 12 with associated severe cerebral amyloid angiopathy (AD-CAA), 14 patients with frontotemporal lobar degeneration (FTLD) associated to amyotrophic lateral sclerosis in two cases, seven with Lewy body dementia (LBD), 10 with progressive supranuclear palsy (PSP), 14 with vascular dementia (VaD), due to atherosclerotic disease and/or CAA, and 12 control individuals who had no clinical history of dementia or stroke (C).

A previously obtained informed consent of the patients or from the nearest family allowed an autopsy for diagnostic and scientific purposes. The brain tissue samples were acquired from the Lille Neuro-Bank of the Lille University that is part of the ''Centres des Resources Biologiques'' and acts as an institutional review board.

One fresh cerebral hemisphere was frozen at -80° C for biochemical examination. The remaining hemisphere, the brainstem, and most of the cerebellum were fixed in formalin for three weeks.

The neuropathological diagnosis was made according a standard procedure and examination of a large number of samples. A whole coronal section of a cerebral hemisphere, at the level of the mammillary bodies, and a horizontal section through the mid-pons and both cerebellar hemispheres was taken for the semi-quantitative evaluation of the cerebrovascular lesions consisting of haematomas, territorial infarcts, LIs and WMCs, micro-bleeds, and micro-infarcts. The mean values for WMCs were the average of the ranking scores: no change (R0), a few isolated (R1), frequent scattered in the centrum semiovale (R2) and forming confluent lesions (R3) of myelin and axonal loss. For the other cerebrovascular lesions, their mean values corresponded to their percentage number.[13]

The brains were classified as AD-CAA, when a majority of β-amyloid stained vessels were present in at least three of the four examined samples and as not-CAA, when absent or scarce, in case of a few stained vessels in one or two slides.[14]

Six coronal sections of a cerebral hemisphere from each brain were submitted to MRI: one at the prefrontal level in front of the frontal horn, one of the frontal lobe at the level of the head of the caudate nucleus, a central one near the mammillary body, a post-central one, a parietal one at the level of the splenium corporis callosi and one at the level of the occipital lobe (Figure 1).

A 7.0-tesla MRI Bruker BioSpin SA with an issuer-receiver cylinder coil of 72 mm inner diameter (Ettlingen, Germany) was used, according to a previous described method.[15] The severity of the WMCs was evaluated in the six brain sections separately in the same way as the neuropathological evaluation. LIs were defined as small-rounded lesions with a diameter between 3 and 15 mm in centrum semiovale, capsula interna, nucleus caudatus, putamen, globus pallidus, and thalamus.[16] The total number and the location of LIs were determined in a similar way by consensus evaluation of three observers (JDR, FA, ND) blinded to the neuropathological diagnosis. The inter-rater reliability resulted in an interclass correlation coefficient of 0.78. The mean values of the WMCs and LIs in the diseased brains were compared to the controls.

Univariate comparisons of unpaired groups were performed with the Fisher's exact test for categorical data. The non-parametric Mann–Whitney U-test was used to compare continuous variables. The significance level, two-tailed, was set at ≤ 0.01 for significant and ≤ 0.001 for highly significant. Values set at ≤ 0.05 and more than >0.01 were considered as marginal significant and not included as relevant due to the relative small sample sizes.

Results

The different disease groups did not show any significant statistical differences regarding age and gender distribution. Arterial hypertension ($p \leq 0.001$)

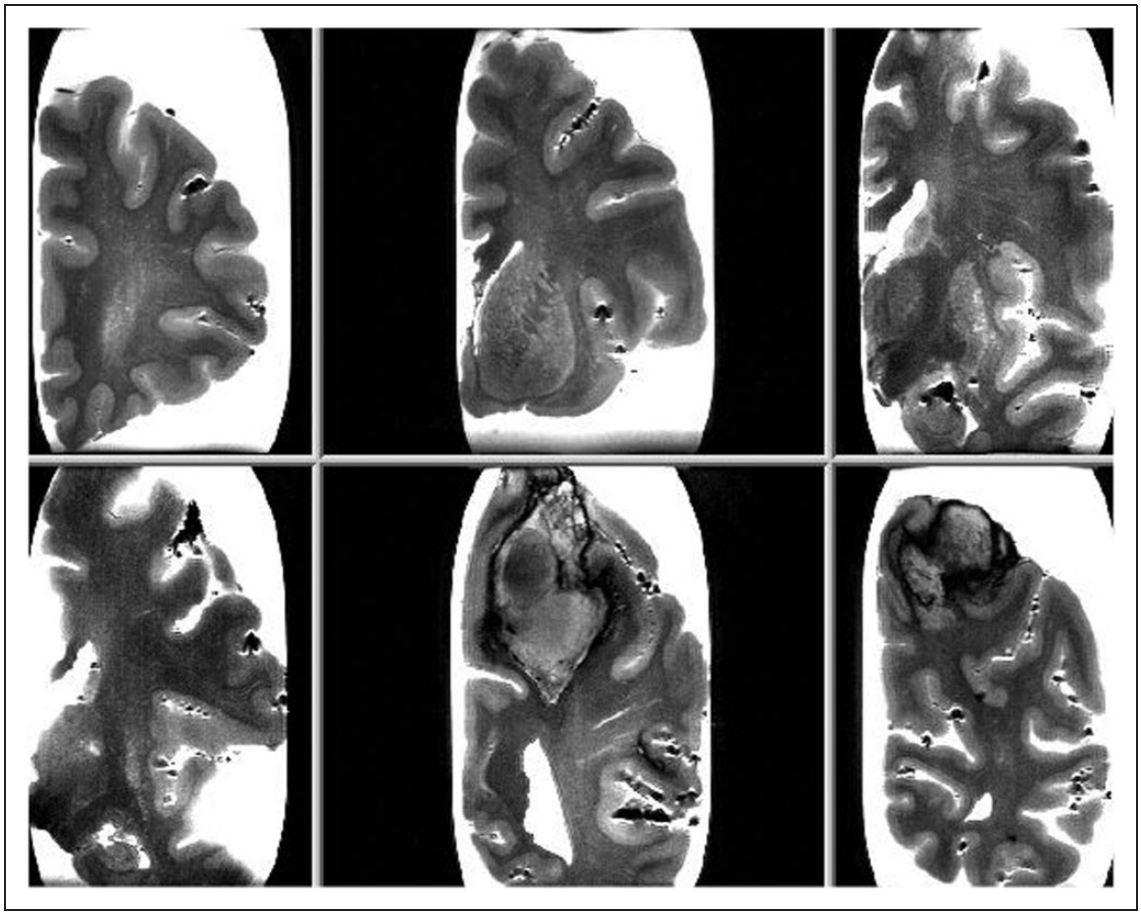

Figure 1. T2 spin echo sequence of the six used coronal sections in a patient with vascular dementia and cerebral amyloid angiopathy. A large parieto-occipital lobar haematoma, many lacunes and diffuse white matter changes are observed.

Table 1. Comparison of median age (interquartile range), gender distribution (%) and vascular risk factors (%) in the control and the disease groups.

Items	Control (n = 12)	AD (n = 15)	AD-CAA (n = 12)	FTLD (n = 14)	LBD (n = 7)	PSP (n = 10)	VaD (n = 14)
Age, years	64	68	66	65	73	74	65
(IQR)	(45–88)	(64–84)	(63–88)	(54–69)	(69–92)	(68–88)	(54–78)
Male gender	58	77	58	50	60	44	75
Arterial hypertension	8	13	8	0	28	20	79**
Diabetes	0	8	8	0	14	10	14
Hypercholesterolemia	17	13	17	7	28	20	50
Smoking	8	0	0	0	14	10	14
Antithrombotic use	8	7	17	0	28	10	86**

AD: Alzheimer's disease; AD-CAA: Alzheimer's disease associated to cerebral amyloid angiopathy; FTLD: frontotemporal lobar degeneration; LBD: Lewy body dementia; PSP: progressive supranuclear palsy; VaD: vascular dementia; ** = p value ≤ 0.001.

and the use of antithrombotic agents ($p \leq 0.001$) were the only more frequently found clinical vascular factors in the VaD patients compared to the controls (Table 1).

On neuropathological examination, WMCs were increased in the AD-CAA ($p \leq 0.01$), the FTLD ($p \leq 0.01$) and the VaD ($p \leq 0.001$) brains. Territorial infarcts ($p \leq 0.01$), haematomas ($p \leq 0.01$), cortical

Table 2. Comparison of the average ranking scores (standard deviations) of the cerebrovascular lesions on the neuropathological examination of the control and the disease groups.

Items	Control (n = 12)	AD (n = 15)	AD-CAA (n = 12)	FTLD (n = 14)	LBD (n = 7)	PSP (n = 10)	VaD (n = 14)
WMC	0.2 (0.6)	1.2 (1.3)	0.9 (0.8)*	1.4 (1.3)*	0.6 (0.5)	1.3 (1.2)	1.9 (1.0)**
Lacunar I	0.0 (0.0)	0.2 (0.6)	0.0 (0.0)	0.3 (0.7)	0.0 (0.0)	0.5 (1.2)	1.3 (1.8)
Territorial I	0.0 (0.0)	0.0 (0.0)	0.1 (0.3)	0.0 (0.0)	0.0 (0.0)	0.3 (0.5)	1.0 (2.1)*
Haematoma	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (1.4)*
CoMIs	0.1 (0.3)	1.2 (1.7)	0.8 (1.1)	0.2 (0.4)	1.5 (2.1)	2.0 (2.3)	3.3 (2.4)**
CoMBs	0.0 (0.0)	0.0 (0.0)	0.2 (0.6)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.5 (2.6)

AD: Alzheimer's disease; AD-CAA: Alzheimer's disease associated to cerebral amyloid angiopathy; FTLD: frontotemporal lobar degeneration; LBD: Lewy body dementia; PSP: progressive supranuclear palsy; VaD: vascular dementia; WMC: white matter changes, I: infarct; CoMIs: cortical microinfarcts; CoMBs: cortical microbleeds; * = p value $\leq$ 0.01; ** = p value $\leq$ 0.001.

Table 3. Average ranking scores (standard deviations) for deep white matter changes on the serial coronal magnetic resonance imaging sections in the control and disease groups.

Items	Control (n = 12)	AD (n = 15)	AD-CAA (n = 12)	FTLD (n = 14)	LBD (n = 7)	PSP (n = 10)	VaD (n = 14)
Prefrontal	0.0 (0.0)	1.1 (0.9)	0.9 (1.0)	1.8 (1.2)**	0.6 (0.5)	0.8 (0.4)	1.8 (0.5)**
Frontal	0.0 (0.0)	0.8 (0.9)	0.9 (0.8)	1.4 (1.3)*	0.8 (0.4)	1.0 (0.8)	2.1 (0.6)**
Central	0.3 (0.6)	0.9 (1.0)	0.9 (1.1)	0.6 (0.7)	0.6 (0.9)	1.3 (1.5)	1.8 (0.7)*
Post-central	0.3 (0.6)	0.7 (0.8)	1.4 (1.1)*	0.5 (1.0)	0.2 (0.4)	1.0 (1.3)	1.9 (0.4)*
Parietal	0.0 (0.0)	0.9 (0.9)	0.6 (1.0)	0.5 (0.9)	0.2 (0.6)	0.8 (1.0)	1.8 (0.7)*
Occipital	0.0 (0.0)	0.8 (1.0)	0.8 (1.0)	0.9 (1.1)	0.2 (0.4)	1.2 (1.3)	2.0 (0.8)**

AD: Alzheimer's disease; AD-CAA: Alzheimer's disease associated to cerebral amyloid angiopathy; FTLD: frontotemporal lobar degeneration; LBD: Lewy body dementia; PSP: progressive supranuclear palsy; VaD: vascular dementia; ** = $\leq$0.001; * = p value $\leq$ 0.01.

micro-infarcts ($p \leq 0.001$) and cortical micro-bleeds ($p \leq 0.01$) were only statistically more frequent in VaD compared to controls (Table 2).

On MRI examination, WMCs were overall increased in the prefrontal, frontal, parietal, and occipital sections ($p \leq 0.001$) and to a lesser degree in the central and post-central sections of the VaD brains ($p \leq 0.01$) (Figure 1) (Table 3). They predominated in the prefrontal ($p \leq 0.001$) and frontal ($p \leq 0.01$) sections of FTLD and in the post-central section of the AD-CAA ($p \leq 0.01$) brains (Figure 2(a) and (b)). The LIs as a whole were increased in the VaD brains ($p \leq 0.01$) and predominated in the centrum semiovale ($p \leq 0.01$) compared to the control and neurodegenerative groups (Table 4) (Figure 3(a) and (b)).

Discussion

The present post-mortem MRI study shows as expected a predominance of WMCs and LIs in VaD.[17] Our MRI rating system appears reliably as there is a good correlation between the incidence and the distribution of the neuropathologic lesions and the MRI findings between the different disease groups. However, LIs are overall somewhat less frequently detected on macroscopic examination of surfaces of the brain sections, compared to the T2-MRI sequence that allowed their detection in the depth of the specimens. Our method is sensitive enough to distinguish by their diameter of $\leq$3 mm LIs from dilated vascular spaces.[18] Compared to 7.0-tesla, 1.5-tesla MRI small cerebrovascular lesions are barely visible,[19] while with 3.0-tesla MRI, their detection still remains low.[20]

Local severe WMCs can also be observed in pure neurodegenerative diseases.

In FTLD, the prefrontal and frontal WMCs, seen on 7.0-tesla MRI, are present where the most severe cortical degeneration occurs, leading to Wallerian degeneration in the white matter.[21,22] Also the presence of cortical microbleeds are linked to the degenerative process (23). However, some recent MRI studies show that WMCs are more distributed than the grey matter lesions, suggesting two separate types of neurodegenerative pathology in FTLD.[24,25]

In AD-CAA brains, WMCs are the most severe in the post-central section, confirming the posterior

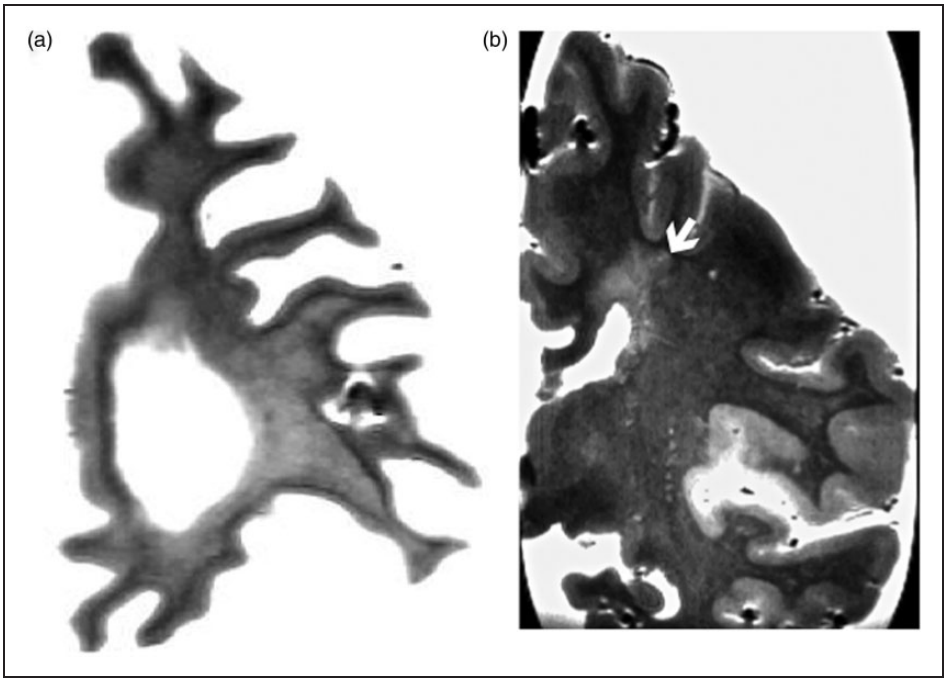

Figure 2. T2 spin echo MRI sequence. (a) Severe cortical atrophy and confluent white matter changes in the prefrontal hemispheric section of a patient with frontotemporal lobar degeneration. (b) Focal confluent deep white matter changes (arrow) in the post-central hemispheric section of a patient with Alzheimer's disease and associated severe cerebral amyloid angiopathy.

Table 4. Average ranking scores (standard deviations) of the lacunar infarcts according to their location on the serial coronal magnetic resonance imaging sections in the control and disease groups.

Items	Control (n = 12)	AD (n = 15)	AD-CAA (n = 12)	FTLD (n = 14)	LBD (n = 7)	PSP (n = 10)	VaD (n = 14)
CS	0.1 (0.3)	0.4 (0.6)	0.5 (1.2)	0.2 (0.4)	0.2 (0.4)	0.8 (1.3)	2.5 (3.3)*
CI	0.0 (0.0)	0.5 (0.9)	0.5 (0.9)	0.4 (0.9)	0.2 (0.4)	0.2 (0.4)	0.9 (1.4)
NC	0.1 (0.3)	0.1 (0.3)	0.4 (0.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.9 (2.1)
P	0.4 (0.5)	0.9 (1.3)	1.2 (1.2)	0.2 (0.4)	0.0 (0.0)	1.5 (2.3)	1.8 (1.3)
GP	0.2 (0.4)	0.1 (0.3)	0.3 (0.5)	0.0 (0.0)	0.0 (0.0)	0.2 (0.4)	0.1 (0.4)
Th	0.1 (0.3)	0.2 (0.4)	0.3 (0.9)	0.2 (0.6)	0.2 (0.4)	0.2 (0.4)	0.9 (1.6)

AD: Alzheimer's disease; AD-CAA: Alzheimer's disease associated to cerebral amyloid angiopathy; FTLD: frontotemporal lobar degeneration; LBD: Lewy body dementia; PSP: progressive supranuclear palsy; VaD: vascular dementia; CS: centrum semiovale; CI: capsula interna; NC: nucleus caudatus; P: putamen; GP: globus pallidus; Th: thalamus; * = p value $\leq$ 0.01.

predominance of the neuropathologic changes in this disease.[26] Most probably they are due to a combination of the neurodegenerative changes and the vascular burden induced by the CAA.[27]

In the present MRI study, no significant WMCs are observed in LBD although previously shown to be moderately present on neuropathologic examination.[28] LBD pathology is considered inversely correlated to the severity of atherosclerosis, infarcts and small-vessel disease.[29]

Although severe WMCs are described on neuropathologic examination[30] and on MRI[31,32] in PSP brains, we are not able to demonstrate a statistical difference compared to controls.

The lack of demonstration in the present study of significant WMCs in LBD and PSP can be due to their small number of samples.

It is still a matter of debate whether the WMCs or the LIs determine most the longitudinal cognitive impairment in small-vessel disease. The quantification methods for in-vivo used MRI are heterogeneous and vary in validation against cognition.[33,34] The progression of cognitive decline is mainly attributed to the WMCs.[35–37] Although LIs in the thalamus are found

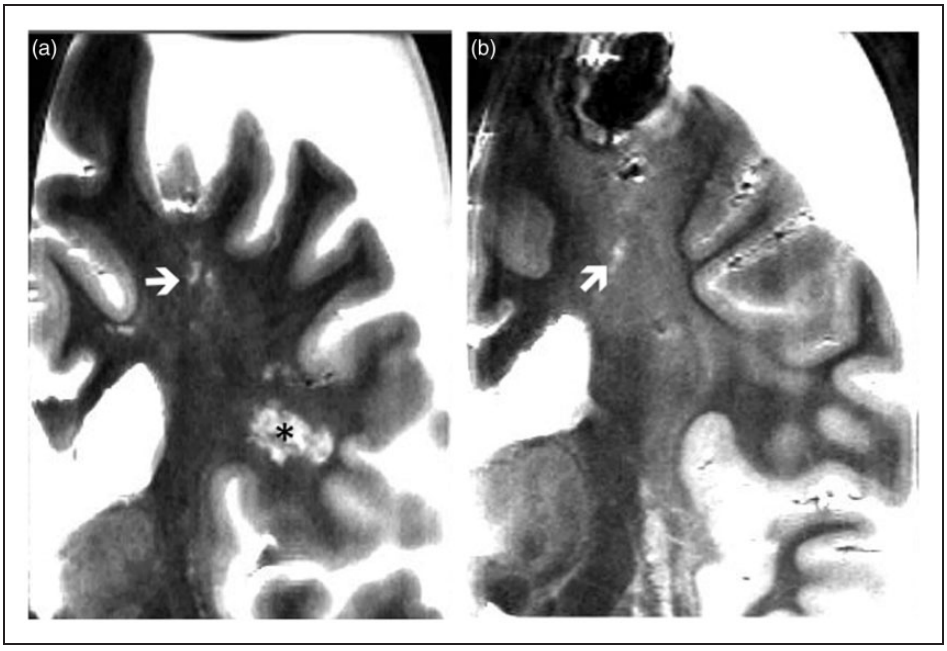

Figure 3. T2 spin echo MRI sequence. (a) Lacunar infarcts (arrow) and focal white matter changes (star) in the centrum semiovale on a central hemispheric section of a patient with vascular dementia. (b) Confluent white matter changes and a lacunar infarct (arrow) in the centrum semiovale on a post-central section of another patient with vascular dementia.

to be associated with cognitive impairment,[38] the contribution of LIs on cognition is considered to be modest.[38]

Our study demonstrates that not only cortical microinfarcts[11] but also LIs in the deep white matter contribute as much as the WMCs contribute to the cognitive impairment of patients with VaD.

In this post-mortem MRI study, VaD appears to be mainly linked to small-vessel disease in the white matter leading to as well WMCs due to chronic ischaemia as to LIs due to small-vessel occlusion.

Provenance

Bo Norrving (Editor-in-Chief) managed the peer review process for this paper. Didier Leys (Vice Editor) was not involved in the peer review of this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Informed consent

A previously written obtained informed consent of the patients or from the nearest family allowed an autopsy for diagnostic and scientific purposes.

Ethical approval

The brain tissue samples were acquired from the Lille Neuro-Bank of the Lille University that is part of the ''Centres des Resources Biologiques'' and acts as an institutional review board.

Guarantor

R Bordet

Contributorship

JDR conceived the study and researched the literature. JDR, FA, ND and RB were responsible for the MRI examinations. VD and CAM performed the neuropathological examinations. CC, FP and DL were involved in the clinical follow-up examination of the patients and the obtained autopsy consent before their death.

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